REMARKS

Claims 6-17 are pending in this application. Claims 1-5 and 18 have been withdrawn as drawn to the non-elected invention. Claims 1-5 and 18 have been cancelled as drawn to the non-elected subject matter. Claims 6-17 are currently under examination in the present application. Claims 6-17 have been rejected. No new matter has been added. Applicants reserve the right to re-file this subject matter in a continuation or divisional application filed during the pendency of this application.

Objection to Specification

The specification was objected to for omission of the priority information for the present application. Applicants have amended the specification to recite the priority information, thereby rendering the objection moot.

Rejection under 35 U.S.C. § 103(a)

Claims 6-17 were rejected under 35 U.S.C. § 103(a) as unpatentable over Martinez *et al.* in view of both Dhadialla *et al.* and Saez *et al.*, as evidenced by Guan *et al.* and Michelotti *et al.*

The examiner suggests that Martinez *et al.* teach an ecdysone receptor chimera comprising the ligand-binding domain of insect ecdysone receptor, and transactivation and DNA-binding domains of the glucocorticoid receptor (GR), glucocorticoid response element, a promoter that is activated by the GR transactivation domain and a target gene. The examiner submits that Martinez *et al.* do not teach modulation of gene expression by a compound of the claimed invention, but suggests that Dhadialla *et al.* teach DTBHIB, a non-steroidal ecdysone agonist used as a pesticide with a structure similar to the claimed formula. However, Dhadialla *et al.* do not teach using DTBHIB to modulate gene expression. The examiner suggests that Saez *et al.* teach that non-steroidal ecdysone analogs, generally used as pesticides, can also be used as activators of the ecdysone system in mammalian cells and transgenic animals, and further suggests that at the time the invention was made, the claimed compound was already known and used as a pesticide (Michelotti *et al.*). Although Michelotti *et al.* do not teach their compound as an ecdysone analog, its structure is similar to the compound of Dhadialla *et al.*, and therefore it would have been obvious to one of skill in the art to use the method of Martinez *et al.* with the compound of Michelotti *et al.* both *in vitro* and *in vivo*, with a reasonable expectation of success. Additionally the examiner suggests that the prior art teaches that compounds having structures similar to the compound of Dhadialla *et al.* could be used as ecdysone analogs, it would have

been obvious to one of skill in the art to use the compound of Dhadialla *et al.* as a central core to generate diverse substituted compounds similar to the compound of Michelotti *et al.* with a reasonable expectation of success.

Applicants contend that Martinez *et al.* teach multiple versions of an inducible chimeric glucocorticoid gene expression system in which the ability of a non-ecdysteroid inducer to induce gene expression is variable. One of the systems actually had low induction levels compared with the same construct under the constitutive 35SCaMV promoter. Upon the addition of the strong VP16 activation domain, induced levels improved however uninduced (background) levels were high. The steroidal agonist murA did not induce and the non-steroidal diacylhydrazine agonist (i.e., tebufenozide) induced but the levels required to achieve good induction levels were too high and the ligand insoluble at the higher levels.

Dhadialla *et al.* teach the insecticidal, ecotoxicological properties and the mode of action of bisacylhydrazines and aromatic non-terpenoidal insecticides. The specific compound disclosed in Dhadialla *et al.* and cited by the examiner, DTBHIB, was a newly discovered compound with **unknown** insecticidal properties. The examiner suggests that the structure of DTBHIB of Dhadialla *et al.* is structurally similar to the amidoketones of the present invention. Applicants contend that the structure of the Dhadialla *et al.* compound is not similar or related to the amidoketones of the present invention as it is clear that DTBHIB is missing pharmacophore elements that are critical to the compounds of the present invention. Specifically the Dhadialla *et al.* compound is missing a ketone group, an aromatic ring and substitutions recited within the present claims.

Applicants submit that Saez *et al.* teach that when over 100 pesticides were tested, and despite diverse chemistry, not one of the compounds was an effective inducer for an ecdysone-regulated gene switch. Saez *et al.* then tested known ecdysone mimics, specifically diacylhydrazines, and found that they were not as good as the steroid PonA, and due to their insolubility precluded their use in extensive *in vivo* analyses. Therefore, Saez *et al.* actually teach away from using non-steroidal ecdysone agonists in ecdysone regulated expression systems.

Furthermore, Applicants contend that the examiner's supposition that at the time of the present invention, the claimed compounds were already known and used as pesticides (Michelotti *et al.*) is not correct. The compound of Michelotti *et al.*, N-acetonylbenzamide, is not a compound claimed in the present invention and is a fungicide, not a pesticide with actions through stimulation of insect ecdysone receptors. Furthermore, the compounds of Michelotti *et al.* were developed to overcome the limitations in the existing benzamides used as fungicides (i.e.

reducing the phytotoxicity of such N-acetonyl substituted benzamides by altering the substituents on the terminal carbon to other than only hydrogen or chlorine). Accordingly, Michelotti *et al.* teach the importance of the addition of halo groups to the terminal carbon in reducing this toxicity and increasing fungicidal activity. This teaches away from the compounds of the present invention, as well as the use of these compounds as ligands for ecdysone receptor-based expression systems.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). For the reasons previously presented above, Applicants contend that Martinez *et al*, Dhadialla *et al.*, Saez *et al.*, Michelotti *et al.* or Guan *et al.* do not teach or suggest all the claim limitations of the present invention, and thus do not support a *prima facie* case of obviousness.

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). In the case of Martinez *et al.* there is no motivation to use non-steroidal agonists as the systems, including ligands tested, were insuffient for use as inducible expression systems given either low induced levels or improved induced levels with high background, and a highly insoluble inducer. In fact, Martinez *et al.* might provide the motivation to one of skill in the art to design a different inducible system with high induction levels, low background and more soluble inducers. Likewise, Saez *et al.* teach away from the use of non-steroidal agonists as Saez *et al.* state that these ligands are not as active as the steroid ponA. Similary, one of skill in the art would not find any motivation in Michelotti *et al.* to use the benzamides as ecdysone agonists as the benzamides are known fungicides, and have structural features (i.e. the presence of halides at the terminal carbon) that would not confer binding to ecdysone receptors. Therefore there is no desirability or motivation to combine any of these teachings. Lastly, the examiner's conclusion that it would have been obvious to one of skill in the art to use the method of Martinez *et al.* with the compound of Michelotti *et al. in vitro* and *in vivo* with a reasonable expectation of success is not supported by the prior art teachings cited. As Saez *et al.* teach away from the use of non-steroidal agonists especially for *in vivo* use, and Michelotti *et al.* specifically teach a class of compounds known for their fungicidal properties, which does not confer binding to ecdysone receptors, not only would one of skill in the art not find motivation or suggestion in the teachings for their combination, but given the difficultly in predicting a compounds ability to act as a proficient ecdysone agonist (i.e. high induction, low background), it would require undue experimentation and low expectation of success.

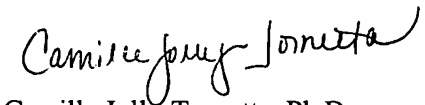
The above combination of prior art fails to teach Applicants' invention and thus fails to establish a *prima facie* case of obviousness. The prior art fails to provide the required motivation, as there is no suggestion in any of the cited art itself to make these combinations or to further modify these combinations.

For the reasons set forth above, Applicants maintain that the combination of the cited prior art, when the teachings are taken *as a whole*, fail to supply the motivation required to set forth obviousness of the claims. Accordingly, withdrawal of the rejection is respectfully requested.

Summary

In view of the foregoing amendments and remarks, Applicants submit that this application is in condition for allowance. Therefore, Applicants respectfully request reconsideration and withdrawal of all of the above rejections, and allowance of the claims.

Respectfully submitted,



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